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Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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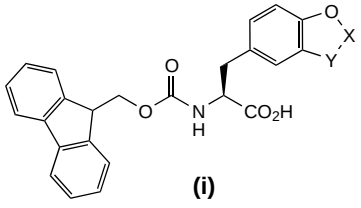
Combinatorial chemistry

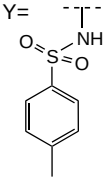
Phosphotyrosine mimetics

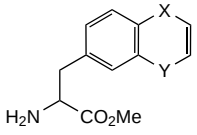
The protein tyrosine phosphatases (PTPases) have an important role in controlling the status of tyrosine phosphorylation and the regulation of cellular function. The ability to selectively inhibit tyrosine phosphatases holds therapeutic potential for the treatment of diseases such as diabetes, cancer and osteoporosis.



(i)

ia: X=CO, Y=NH
ib: X=SO2, Y=



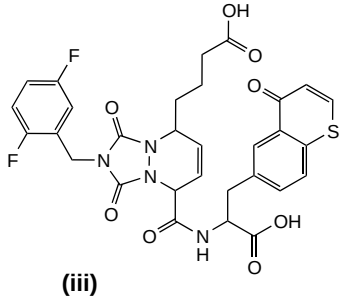


(ii)

iia: X=O, Y=CO
iib: X=S, Y=CO
iic: X=CMe_2, Y=CO
iid: X=O, Y=SO_2

Two classes of phenylalanine derivatives, (**i**) and (**ii**), have been identified [1] and research is ongoing. The type **i** derivatives were designed to mimic a phosphorylated tyrosine, whereas, the type **ii** derivatives include aryl substituents, similar to a 1-benzothiopyran-1,1,4-trione moiety, previously thought to be a selective, irreversible inhibitor of protein tyrosine phosphatase 1B [2]. These phosphotyrosine mimetics were successfully incorporated into a small library, containing triazolopyridazine β-strand templates [3].

Screening for inhibition of four phosphatases (CD45, LAR, TCPP, and PTP1B) was accomplished by fluorometric assays, using 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP, Molecular Probes) as substrate. Several moderately potent analogues were obtained (upto 85% inhibition at 10 μM sample concentration) and selectivity against the tyrosine phosphatases assayed was achieved, with the type **ii** phosphotyrosine mimetic providing the best activity. See for example (**iii**)



(iii)

with 85% inhibition against TC-PTP. This work has generated moderately potent and selective tyrosine phosphatase inhibitors, and further work in this area is warranted.

1 Blaskovich, M.A. *et. al.* (2003) Design and synthesis of phosphotyrosine mimetics. *Bioorg. Med. Chem. Lett.*13, 2083–2085
2 Ham, S.W. *et. al.* (1999) Selective inactivation of protein tyrosine phosphatase PTP1B by sulfone analogue of naphthoquinone. *Bioorg. Med. Chem. Lett.* 9, 185–186
3 Kahn, M. *et. al.* (1998) Highly efficient and versatile synthesis of libraries of constrained β-strand mimetics. *Bioorg. Med. Chem. Lett.* 8, 2321–2326

Histamine H_3 receptor antagonists

To date, four distinct receptors (H_1–H_4), through which histamine exerts its effects in both the CNS and the periphery, have been identified. Histamine H1 and H2 receptor-blockers are important medicines in clinical use today. The H_3 receptor, primarily located in the CNS, is a presynaptic receptor that modulates the production and release of histamine. Blockade of this receptor leads to increased levels of histamine and other neurotransmitters throughout the brain *via* effects on pre- and post-synaptic H_3 heteroreceptors. The wide distribution of H_3 receptors in the mammalian CNS indicates a physiological role for this receptor, therefore, its therapeutic potential as a novel drug development target has been proposed for indications

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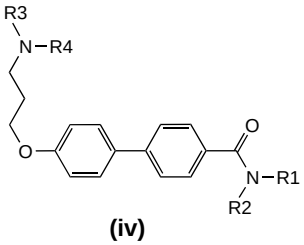
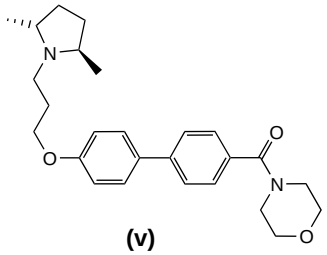


(iv)

associated with neurological disorders, such as attention-deficit hyperactivity disorder, Alzheimer's disease, Parkinson disease and epilepsy, as well as metabolic disorders such as obesity.

A series of biaryl derivatives has been investigated in an attempt to develop selective H_3-blockers [4]. A small library of 49 biphenyl-*O*- propylamine amides (**iv**) was synthesized as singletons in solution; the resulting products were purified using high-throughput HPLC-MS techniques and assayed in a binding experiment, using cloned human H_3 and rat cortex H_3 receptors. A number of potent inhibitors were found, one of the most potent being **v**, which possessed a pK_i value of 9.31 against hH_3 and a pK_i value of 8.78 against rH_3. This compound



(v)

demonstrated excellent selectivity towards histaminergic receptors (pK_i = 5.63 at hH_1 and pK_i = 5.00 at hH_2 and hH_4 receptors). This work has generated rapid SAR and identified potent ligands for both human and rat H_3 receptors, and, thus, further research into the use of compounds such as these for studies in various CNS disorders is warranted.

4 Faghih, R. *et. al.* (2003) Synthesis and SAR of aminoalkoxy-biary-4-carboxamides: novel and selective histamine H_3 receptor antagonists. *Bioorg. Med. Chem. Lett.*, 13, 1325–1328

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